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Occurrence of Cardiac Malformations in Relatives of Children With Transposition of the Great Arteries

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Transposition of the great arteries (TGA) is the most common cyanotic cardiac malformation, representing 5–7% of all cardiac malformations. Previous estimates of the frequency of cardiac malformations in sibs of probands range from 0–1.7%. This study ascertained the frequency of congenital cardiac malformations in relatives of 271 probands with TGA, who were grouped according to the type of TGA present. These include dextro (d-TGA), levo (l-TGA), complex TGA, and asplenia with TGA.

In the d-TGA cases there were 369 sibs, one of whom had a cardiac malformation (0.27%). There were 50 sibs in the l-TGA group, with one sib having a cardiac malformation (2.00%). Cardiac malformations were found in 2 of 143 (1.40%) sibs of the complex TGA index cases, and 1 of 50 (2.00%) sibs in the asplenia with TGA group. The overall recurrence risk of cardiac malformations in sibs of TGA probands was 0.82%. Cardiac malformations in parents of probands were found in 0.29% of d-TGA, 0% of l-TGA, 1.54% of complex TGA, and 0% of asplenia with TGA, giving an overall parental occurrence of 0.55%. This is the first study to provide information on the different types of TGA in evaluating sib occurrence. It provides necessary genetic counseling information for families of probands with TGA.

KEY WORDS: transposition of great arteries, asplenia, familial congenital heart malformations

INTRODUCTION

Congenital cardiac malformations are present in 0.8% of live births [Pierpont and Moller, 1986]. Transposition of the great arteries (TGA) is one of the more common cardiac malformations in this group, accounting for 4–10% of all cases [Fyler et al., 1980; Hoffman and Christianson, 1978]. Furthermore, it is the most common cause of cyanosis in the first year of life. There is also a sex difference in the occurrence of TGA, with a male:female ratio of 1.8:1 [Freed and Castaneda, 1990], in contrast to most cardiac malformations where a sex predilection is not found. TGA is usually not associated with known genetic syndromes, other phenotypic abnormalities, or chromosomal anomalies; extracardiac malformations are seen in only 9% of children with TGA [Liebman et al., 1969].

Recurrence risks for cardiac malformations in sibs of children with TGA have been reported to be between 0% and 1.7% [Boughman et al., 1987; Briard et al., 1984; Nora and Nora, 1978; Sanchez-Cascos, 1978]. Most of these studies have involved a relatively small number of index cases and have considered all types of TGA as a single group. No information about cardiac abnormalities for offspring of parents with TGA has been published, likely because the first survivors of corrective surgical procedures are now reaching adulthood. The current study was designed to ascertain the frequency of cardiac malformations in sibs and relatives of children with different types of TGA and to identify possible teratogenic agents.

MATERIALS AND METHODS

Index cases of TGA were identified though the files of the Division of Pediatric Cardiology at the University of Minnesota. Inclusion in this study was limited to those individuals who had been evaluated by a pediatric cardiologist at the University of Minnesota with a primary diagnosis of TGA between 1965 and 1991. A total of 408 cases of TGA were identified. Confirmation of the cardiac malformation was made by one of the following methods: echocardiography, surgery, cardiac catheterization, or autopsy. Index cases were grouped as dextro (d-TGA), levo (l-TGA), complex TGA, and asplenia with TGA ("asplenia"). Complex TGA in this study was defined as TGA with the occurrence of a single ventricle, tricuspid atresia, or double outlet right ventricle. As-

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plenia cases were grouped as a separate category because cardiac malformations are a recognized part of the asplenia/polysplenia spectrum.

Our initial contact with each family was by questionnaire or telephone. If unsuccessful, the family's physician was contacted and their assistance in locating the individual was requested. Other methods for location included contacting relatives, post offices, and motor vehicle registration records. Information was obtained from index cases (if >21 years) or their parents (if <21 years), regarding the occurrence of cardiac malformations in sibs, parents, and relatives (second-degree relatives including grandparents, aunts, uncles, nephews, nieces, and half-sibs; third-degree relatives including first cousins, great-grandparents, great-aunts, and great-uncles; and greater than third-degree relatives). Information was also obtained about the results of all pregnancies and first trimester maternal medications during the pregnancies with the probands. Any families reporting maternal diabetes mellitus were excluded from this study because of the recognized association with congenital cardiac malformations in offspring.

Documentation of cardiac malformations in relatives of index cases was obtained from records of echocardiography, cardiac catheterization, autopsy, or surgery. A report of either a cardiac murmur without a diagnosis, or a "blue baby" who died without autopsy was not accepted as an occurrence of a congenital cardiac malformation. Some families reported relatives with "congenital heart disease," which could not be confirmed by the above criteria, and these were not included in the final analysis. All reports of patent ductus arteriosus were confirmed as not associated with prematurity.

RESULTS

The search outcome for the families of probands in the TGA categories (d-TGA, l-TGA, complex TGA, asplenia with TGA) is presented in Table I. Of the 408 index cases identified for the study, 117 were lost to follow-up, 4 medical exclusions were made due to maternal diabetes mellitus, and 16 families refused to participate.

In retrospective studies of familial risk, one potential complicating factor on the validity of the results is that of sampling bias in the index case population. The families participating in the study may not be truly representative of the overall index population. A presentation of the estimate of sampling error is made in Table II. The proportion of families (Study Families) for each group of TGA was similar to the original distribution of TGA families (Index Cases). In addition, study families might be overrepresented by those who are more inclined to respond because they have affected relatives. Whereas the total reply rate for all TGA types was comparable (63.3–76%), the number of families who indicated a relative with a congenital cardiac malformation was more variable (15.8–38.5%).

The most common cardiovascular malformation associated with d-TGA, l-TGA, or complex TGA in our study was ventricular septal defect, seen in 39.7% of all probands (data not shown). Pulmonary stenosis was observed in 27.4% of all probands, and coarctation of the aorta was the third most common associated malformation, seen in 7.9% (data not shown). However, coarctation of the aorta was seen only in the d-TGA and complex TGA groups; none of the l-TGA probands had this associated malformation.

d-TGA

Of the 168 probands, 113 were male and 55 were female, confirming the predominance of males with TGA. There were 369 sibs in this group, and one (0.27%) had a cardiac malformation (hypoplastic left heart syndrome) (Table III). One of the 336 parents (0.29%) had a cardiac malformation: a father had l-TGA with atrial septal defect, ventricular septal defect, and pulmonary stenosis. Four second-degree relatives had cardiac malformations: tetralogy of Fallot (1), patent ductus arteriosus (1), hypoplastic right pulmonary artery (1), and aortic atresia (1). Seven third-degree relatives had cardiac malformations: ventricular septal defect (2), atrial septal defect (1), bicuspid aortic valve (2), hypoplastic right ventricle (1), and aortic stenosis (1). Eighteen greater than third-degree relatives had cardiac malformations: l-TGA (1), d-TGA (2), tetralogy of Fallot (3), hypoplastic left heart syndrome (1), endocardial cushion defect (1), patent ductus arteriosus (2), ventricular septal defect (2), atrial septal defect (2), atrial septal defect with ventricular septal defect (1), interrupted aortic arch type B (1), aortic stenosis (1), and pulmonic stenosis (1). In addition to the above affected relatives, some individuals in these families reported cardiac malformations that could not be confirmed. These included two sibs and one parent.

Of 611 pregnancies in 168 mothers of the d-TGA probands, there were 73 spontaneous abortions (11.9%), and one stillbirth (0.2%). There were 15 adults with d-TGA who had eight offspring; none of the offspring had a cardiac defect. Fourteen mothers reported taking either oral contraceptives (1 mother) or Bendectin (13 mothers) during the first trimester of pregnancy, and one mother was given gamma globulin during the first trimester.

TABLE I. Search Outcome

	d-TGA	l-TGA	Complex TGA	Asplenia
Subjects participating	168	19	65	19
Lost to follow-up	81	8	22	6
Medical exclusions	2	0	2	0
Refused participation	7	3	6	0
Total index cases	258	30	95	25

TABLE II. Estimate of Sampling Error

Cardiac malformation[a]	Index cases (n = 408)	Study families (n = 271)	Total reply d-TGA (n = 258)	Total reply l-TGA (n = 30)	Total reply CpTGA (n = 95)	Total reply asplenia (n = 25)	Positive replies[b] d-TGA (n = 168)	Positive replies[b] l-TGA (n = 19)	Positive replies[b] CpTGA (n = 65)	Positive replies[b] asplenia (n = 19)
d-TGA	258 (63.2%)	168 (62.0%)	168 (65.1%)				43 (25.6%)			
l-TGA	30 (7.4%)	19 (7.0%)		19 (63.3%)				3 (15.8%)		
CpTGA	95 (23.3%)	65 (24.0%)			65 (68.4%)				25 (38.5%)	
Asplenia	25 (6.1%)	19 (7.0%)				19 (76.0%)				7 (36.8%)

[a] d-TGA = d-transposition; l-TGA = l-transposition; CpTGA = complex transposition.
[b] Indicates families reporting relatives with congenital cardiac malformation.

l-TGA

Of the 19 probands with l-TGA, 12 were male and 7 were female. There were 50 sibs in this group, and one (2.0%) had a cardiac malformation (patent ductus arteriosus not associated with prematurity) (Table III). None of the parents had a cardiac malformation. One greater than third-degree relative reported a cardiac malformation: d-TGA with tricuspid atresia.

Of 82 pregnancies in 19 mothers of the l-TGA probands, there were 12 spontaneous abortions (14.6%), and one stillbirth (1.2%). There were nine adults with l-TGA who had 10 offspring; none with a cardiac malformation. Two mothers reported taking Bendectin during the first trimester of pregnancy, and one mother reported first trimester exposure to Synthroid.

Complex TGA

The probands in the complex TGA group had the following cardiac malformations in addition to TGA: 38 with single ventricle, 15 with origin of both great vessels from the right ventricle, 10 with tricuspid atresia, and 2 with multiple other cardiac anomalies. Of 65 probands with complex TGA, 43 were male and 22 were female. There were 143 sibs in this group, and 2 (1.40%) had a cardiac malformation (Table III), one with truncus arteriosus, the other with d-TGA. Two of the 130 parents (1.54%) had a cardiac malformation: one mother with aortic stenosis, and one mother with mesocardia and interruption of the inferior vena cava with azygous continuation. Four second-degree relatives had cardiac malformations: ventricular septal defect (2), atrial septal defect (1), and aortic valvular insufficiency (1). One third-degree relative had a cardiac malformation, bicuspid aortic valve with aortic valvular insufficiency. Four greater than third-degree relatives had cardiac malformations: atrial septal defect (2), d-TGA (1), and tetralogy of Fallot (1). One sib had a suspected but unconfirmed cardiac malformation.

Of 230 pregnancies in 65 mothers of the complex TGA probands, there were 20 spontaneous abortions (8.7%), and 2 stillbirths (0.9%). There were 11 adults with complex TGA who had six offspring; none of the offspring have a cardiac defect. Five mothers reported taking Bendectin during the first trimester of pregnancy, one mother reported a first trimester exposure to Synthroid, and one mother was given gamma globulin during the first trimester.

Asplenia With TGA

Of the 19 probands with asplenia and TGA, 13 were male and 6 were female. There were 50 sibs in this group, and one (2.0%) had a cardiac malformation (asplenia with d-TGA and single ventricle) (Table III). None of the parents had a cardiac malformation. Two third-degree relatives had cardiac anomalies: l-TGA with single ventricle (1), and patent ductus arteriosus (1) not due to prematurity. Two greater than third-degree relatives had cardiac malformations: tetralogy of Fallot (1), and single ventricle with pulmonary atresia and mitral valve atresia (1). Three second-degree relatives had suspected but unconfirmed cardiac malformations.

TABLE III. Occurrence of Congenital Cardiac Malformations in Relatives of Probands With TGA

Cardiac malformation[a]	Probands	Total sibs	Concordant CCM[b]	All CCM	Parents with CCM[c]	2° Relatives with CCM[c]	3° Relatives with CCM[c]	>3° Relatives with CCM[c]
d-TGA	168	369	0	1 (0.27%)	1 (0.29%)	4	7	18
l-TGA	19	50	0	1 (2.00%)	0	0	0	1
CpTGA	65	143	2 (1.40%)	2 (1.40%)	2 (1.54%)	4	1	4
All TGA	252	562	2 (0.36%)	4 (0.71%)	3 (0.59%)	9	8	23
Asplenia	19	50	1 (2.00%)	1 (2.00%)	0	0	2	2

[a] d-TGA = d-transposition; l-TGA = l-transposition; CpTGA = complex transposition.
[b] Concordant CCM for TGA: tetralogy of Fallot, transposition of the great arteries, truncus arteriosus.
[c] CCM = Congenital cardiac malformations.

Of 76 pregnancies in 19 mothers of the asplenia probands, there were 7 spontaneous abortions (9.2%), and no stillbirths. None of the asplenia with TGA probands are adults, consequently no offspring were reported. No first trimester pregnancy medications were reported by mothers in this group.

DISCUSSION

In the past, congenital cardiac malformations have been ascribed to multifactorial or polygenic inheritance [Nora and Nora, 1983]. However, in recent years it has become apparent that single major genes may be involved in the causation of some cardiac malformations, such as endocardial cushion defects [Cousineau et al., 1994] or patent ductus arteriosus [Sletten and Pierpont, 1995]. Additionally, conotruncal cardiac malformations, either isolated or in association with DiGeorge syndrome or velocardiofacial syndrome have been found to be associated with microdeletions of chromosome 22q11 [Driscoll et al., 1993; Goldmuntz et al., 1993; Wilson et al., 1993]. Thus the etiology of many types of cardiac malformations, including TGA, is yet to be described.

Limited information on recurrence risks of cardiac malformations in sibs of individuals with TGA has previously been available. This study identified a recurrence risk in sibs of children with d-TGA (0.27%), l-TGA (2.00%), complex TGA (1.40%), and asplenia with TGA (2.00%). The combined risk for cardiac malformations in sibs of children with all types of TGA is 0.82%. This confirms that the rate of occurrence of cardiac malformations in sibs of TGA probands is similar to previous reports in smaller studies [Boughman et al., 1987; Nora and Nora, 1978; Sanchez-Cascos, 1978]. Although this study also examined families of probands with asplenia and TGA, this particular group of individuals fits into the spectrum of lateralization defects or heterotaxia. Families have been reported in recent years that document autosomal recessive, autosomal dominant or X-linked inheritance [Alonso et al., 1995; Casey et al., 1993]. Thus in asplenia with TGA, Mendelian inheritance patterns can play a role and each family should be considered separately for genetic counseling. The family described here with two affected children with asplenia and TGA could represent one where a Mendelian pattern is present.

This study has also identified cardiac malformations in parents of children with TGA: 0.29% for d-TGA, 1.54% for complex TGA, 0% for l-TGA, and 0% for asplenia with TGA; the combined parental occurrence was 0.55%. One previous study [Boughman et al., 1992] found an incidence of 5.3% (one of 19 parents), using echocardiographic examination. In our study, none of 35 adult probands with TGA of all types had a child with a cardiac malformation (24 total offspring). However, one proband with d-TGA was found to have a father with l-TGA. Thus more information is needed in the future to evaluate offspring risk of cardiac malformations.

We did not find a specific association between maternal first trimester medications and cardiac malformations in the study families. Medications reported most often used by mothers in the study were Bendectin or another unspecified nausea medication, which was taken by 7.4% of all mothers of children with TGA. In a previous study evaluating the effects of Bendectin use during early pregnancy and the relation to congenital heart disease in the babies [Zierler and Rothman, 1985], 17% of mothers (in both the study and control groups) reported using the drug. No association or increased incidence of cardiac malformations was found. In a large prospective study involving 31,564 newborns, Shiono and Klebanoff [1989] found no increase in the overall incidence of major malformations in children exposed to Bendectin prenatally. In particular, no association with cardiac malformations was shown.

Only one mother in all groups of TGA of our study reported taking oral contraceptives during early pregnancy. Whereas several studies [Levy et al., 1973; Nora and Nora, 1973] have suggested a possible association between prostagen-estrogen compounds found in oral contraceptives and cardiac malformations, others [Yasuda and Miller, 1975] have not supported such an association.

These results provide additional necessary genetic counseling information for families of probands with different types of TGA. Future follow-up with these TGA probands will yield additional information regarding occurrence of cardiac malformations in their offspring. Fetal echocardiography can be offered for prenatal diagnosis of cardiac malformations during

pregnancies in those families either having one child with TGA, or with one parent affected by TGA.

A recent study of microdeletions of chromosome 22q11 and TGA [Melchionda et al., 1995] found a deletion in 4 of 32 children with TGA, most of whom showed clinical features consistent with the spectrum of velocardiofacial syndrome. They concluded that a small number of patients with TGA can have microdeletions at the 22q11 locus. Whereas the prevalence of 22q11 microdeletions in TGA is not known, microdeletion studies of individuals with TGA may be warranted to identify those who have a higher risk (up to 50%) for future offspring with cardiac malformations, or possibly affected parents who have not been identified.

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